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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Youlin Lin
Serial No. 338,382
Filed January 11, 1982
For: Chemical Compounds Group Art Unit 126
Examiner: B. Helfin

DECLARATION

I, George Brooke Hoey, of 701 Moundale Drive, Ferguson, Missouri, hereby declare as follows:

1. I hold an A.B. Degree in Chemistry from Emory University (1949) a M.A. Degree in Organic Chemistry from Emory University (1950) and a P.H.D. Degree in Organic Chemistry from Emory University (1954) . I have been employed by Mallinckrodt, Inc., assignee of the above-identified patent application, since 1957 and am presently Director of Research, for the Research and Development Division, Medical Products Group of Mallinckrodt. I have performed research and development work in the field of x-ray contrast media including non-ionic contrast media, and am familiar with the above-identified patent application which is directed to the compound N,N-bis-(2,3-dihydroxypropyl)-5-[N(2-hydroxyethyl)-glycolamido]-2,4,6-triiodoisophthalamide.

2. The utility of non-ionic x-ray contrast agents is based, among other things, on high water solubility. The diagnostically useful concentrations of contrast media solutions for human use lie in the range of 20-40% w/v iodine (room temperature) requiring therefore that the non-ionic contrast media molecule possess a water solubility sufficient to give these concentrations of iodine. It is well known in this art, that the exact

prediction of water solubility of candidate non-ionic x-ray contrast agents on the basis of scientific theory, or an empirical "rule of thumb", or a structual relationship has never been demonstrated. In my opinion, it is not possible to predict with any degree of certainty the water solubility of candidate non-ionic x-ray contrast media.

This point is amply illustrated both in the attached paper by Pitre and Felder and in the attached paper of Hoey, et al., wherein several series of non-ionic x-ray contrast agents are reviewed. In table II of the Felder-Pitre article, the water solubility of iopamidol and closely related analogs are given. Compound 5 in this table is iopamidol with a water solubility of 90g/100ml at 25°C. The closely analogous (unsymmetrical) isomeric analog, Compound 11, displays a solubility of 12g/100ml in water at 25°C. Likewise, Compound 6, symmetrical but isomeric with iopamidol, shows a water solubility of 13g/100ml.

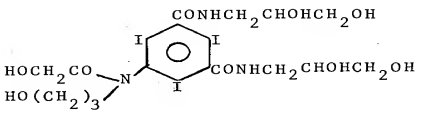
In the Hoey et al. article, summary data are given for six series of non-ionic compounds. In each of these series, the water solubility varied widely (1 to 100% w/v, see Table III, page S291). Similar examples are found in literature for ionic x-ray contrast media (see review by Hoey, Wiegert and Rands in Radiocontrast Agents, Vol. 1, pages 23 - 132, 1971).

Additionally, Pitre and Felder in Table II disclose three candidate hydroxyacetamido non-ionic compounds (Compounds, 1, 2 and 3). All three were essentially water insoluble. Based on this published

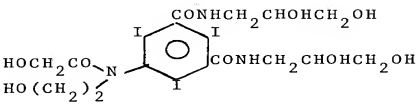
literature, one skilled in the art would not predict, in my opinion, that hydroxyacetamido derivatives of amine-triiodoisophthalamide non-ionic compounds to be useful as x-ray contrast media.

It is also interesting that these authors state "asymmetric amides (i.e., those with two different amide substituents) were found to be generally less water soluble than the symmetric ones". Speck on the other hand indicates that asymmetric amides are more water soluble than symmetric amides. This again demonstrates that the water solubility of non-ionic x-ray contrast media is unpredictable , especially predictions based on structure.

A close analog to MP-328 was synthesized and its structure is set out below along with that of MP-328.



MP-420



MP-328

This compound could be predicted to have approximately the same water solubility as MP-328. In actual fact, its water solubility is less than 25% w/v (solubility of MP-328 is in excess of 100% w/v). This, once again, illustrates the inability to predict water solubility on the basis of structure.

In summary, based upon my experience as an organic chemist with non-ionic x-ray contrast media, it is my opinion that there are few generalizations which apply to the design of such media and that it is difficult to synthesize compounds which are highly water soluble. Also,

in my opinion, it is impossible to predict whether a given compound will be water soluble prior to the synthesis and testing of the compound.

3. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified patent application or any patent issuing thereon.

George Brooke Hoey

George Brooke Hoey

Dated:
11/4/82

A B S T R A C T*

CLINICAL EXPERIENCE WITH IOGULAMIDE:

A NEW NONTOXIC MYELOGRAPHIC AGENT

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Iogulamide is a new nonionic contrast agent developed primarily for intrathecal use. Comparative preclinical animal studies demonstrated an acute safety profile significantly superior to that of metrizamide. The clinical trials for lumbosacral myelography with iogulamide in doses of 170, 200 and 230 mgm I% will be described. Initial experience with 11 patients produced technically satisfactory diagnostic studies and no observable adverse side effects. The potential advantages of this new intrathecal contrast agent will be emphasized.

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